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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/001,934 | 11/15/2001 | Zoltan Nagy | GPCG-P01-003 | 8886 |

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ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/001,934 | NAGY ET AL | |
| | Examiner | Art Unit | |
| | Karen A Canella | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *7-29,33-65,67,70-87 and 92-129* is/are pending in the application.

4a) Of the above claim(s) *39-42,44-54,57,58,64,65 and 96-116* is/are withdrawn from consideration.

5)☒ Claim(s) *67 and 126-129* is/are allowed.

6)☒ Claim(s) *7-19, 22-29, 33-38, 43, 55, 56, 59-63, 73-77, 80-87, 92-95, 117-118, 122, 124 and 125* is/are rejected.

7)☒ Claim(s) *20,21,70-72,78,79,119-121 and 123* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Jan. 28, 2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-6, 30-32, 66, 68, 69, and 88-91 have been canceled. Claims 7-11, 13-18, 20, 22-28, 33-38, 43, 55, 59-63, 67, 70, 71, 73-78, 80, 81, 82-86 and 92 have been amended. Claims 117-129 have been added. Claims 39-42, 44-54, 57, 58, 64, 65 and 96-116 remain withdrawn from consideration. Claims 7-29, 33-38, 43, 55, 56, 59-63, 67, 70-87, 92-95 and 117-129 are under consideration.

2. Text of sections of Title 35, US Code not found in this action can be found in a previous action.

3. The rejection of claim 38 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record.

Claim 38 is drawn to the compositions of claims 22-29, wherein the antigen-binding sites are cross-linked to a polymer. It is well known in the art that a paratope minimally comprises a CDR region, and in some cases comprises additional residues in the variable chain regions (Amit et al Science Vol 233 747-753 1986). When given the broadest reasonable interpretation, claim 38 can be read as minimally comprising only the CDR regions of the antibody, which are cross-linked to a polymer. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor of the CDRs as a result of the cross-linking to the polymer,

may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that a polymer upon which CDRs from the heavy and light chain variable regions of an antibody are attached in unspecified order would have the required binding function. The specification provides no direction or guidance regarding how to produce CDR regions cross linked to a polymer which will retain the binding activity of the variable regions from which they were derived. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. One of skill in the art would neither expect nor predict the appropriate functioning of the antigen-binding regions cross linked to a polymer as claimed. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to make and use the claimed invention. Amendment of claim 38 to dependent on claims 22-29 has not obviated this rejection.

4. Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 13-16 require specific cell lines. It is unclear whether the exact cell lines possessing the identical properties of KARPAS-422. GRANTA-519, LG2 and PRIESS are known and are publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. It is unclear that one of skill in the art could derive cell lines identical to those claimed. Because one of ordinary skill in the art could not be assured of the availability to practice the invention as claimed in the absence of the availability of the claimed cell lines, a suitable deposit of the cell line for patent purposes, evidence of public availability of the cell lines, or evidence of reproducibility without undue experimentation of the claimed cell lines is required.

If the deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposits have been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CRF 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his/her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(C ) the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced should they become non-viable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit. If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited cell lines are the same as those described in the specification as filed, stating that the

deposited cell lines were the same as described in the specification and were in the applicant=s possession at the time the application was filed.
Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Applicants amendment of claims 13-16 with deposit numbers from other patents does not satisfy the requirements for a deposit in the instant application. Applicant's arguments that the cell line of LG2 is known in the art is also unpersuasive, as the availability of said cell line must be enforced for the life of a patent which would issue from the instant application. Arguing that a cell line is known in the art does not guarantee that said cell line would be freely available to the public.

5. Claims 7-19, 22-29, 33-38, 43, 55, 56, 59-63, 73-77, 80-87, 92-95, 117-118, 122, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Independent claims 22, 23, 24, 26 and 28 are drawn to a composition comprising an antibody-based antigen binding domain of human composition with binding specificity for an antigen expressed on the surface of a human cell. Independent claims 80, 81, 82, 84 and 86 are drawn to a composition comprising an antibody-based antigen binding domain of human composition with binding specificity for an MHC class II antigen. Thus claims 22, 23, 24, 26 and 28 are drawn to a genus of antigens expressed on the surface of a human cell and claims 80, 81, 82, 84 and 86 are drawn to a genus of MHC class II antigens. The specification discloses composition comprising an antibody based antigen binding domain of human composition with binding specificity for HLA-DR as an antigen. The disclosure of antibody based antigen binding domain of human composition with binding specificity for HLA-DR as an antigen does not adequately describe the genus of antigens expressed on the surface of a human cell, or the genus of MHC class II antigens because each genus encompasses members which differ in structure and function from the HLA-DR antigens. Because the genuses of antigens to which the instant

compositions specifically bind lack adequate written description, the claimed compositions also lack adequate written description.

6. Claims 7-19, 22-29, 33-38, 43, 55, 56, 59-63, 73-77, 80-87, 92-95, 117-118, 122, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising antibody-based binding domains that specifically bind to the HLA-DR antigen, does not reasonably provide enablement for antibody-based antigen-binding domains with binding specificity for an antigen-expressed on the surface of a human cell or antibody-based antigen-binding domain with a binding specificity for a human class II antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Independent claims 22, 23, 24, 26 and 28 are broadly drawn to compositions comprising a polypeptide comprising an antibody-based antigen-binding domain of human composition with binding specificity for an antigen-expressed on the surface of a human cell wherein treating the cells expressing said antigen with an antibody comprising said antigen-binding domains causes or leads to killing of said cells in a manner wherein neither cytotoxic entities nor immunological mechanisms are needed for said killing. Independent claims 80, 81, 82, 84 and 86 are broadly drawn to an antibody-based antigen-binding domain with a binding specificity for a human class II antigen wherein treating cells expressing said antigen with the antibody-based antigen binding domain causes or leads to suppression of an immune response. The specification teaches only antibodies or antibody-based antigen binding compositions wherein the antigen is HLA-DR and the resulting death of the cell expressing said antigen by a non-cytotoxic, non-immunological mechanism. The art recognizes several murine antibodies which bind to HLA-DR and induce cell death by the claimed mechanism (Truman et al, International Immunology, 1994, Vol. 6, pp. 887-896). There is no support in the art or the specification for other HLA class II antigens or other surface antigens which mediate this type of cell death. Drenou et al (Journal of Immunology, 1999, Vol. 163, pp. 4115-4124, cited in the previous Office action) teach that the cytotoxic action of anti-HLA-DR antibodies on B cells is due to an innate pre-programmed process of said cells resulting in the death of the B cells by a pathway that was not a classical

apoptotic pathway. Thus, there is no support in the art or the specification for other cell surface antigens which are not HLA-DR, modulating the death of the cell by the non-classical apopotic pathway described by the specification and by Drenou et al. The scope of the claims must be commensurate with the scope of the enablement set forth, and given he lack of teaching in the art or the specification on other cell surface antigens which are not HLA-DR having the ability to mediate cell death by a mechanism that does not involve cytotoxic moieties nor immunological mechanisms such as ADCC or CDC, one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed compositions.

7. Claims 20, 21, 70-72, 78, 79, 119-121, 123 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/12/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER